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(54) MEDICINAL COMPOSITIONS WITH RELIEVED BITTERNESS, ETC.

(57) Compositions wherein bitterness, etc. of a drug have been relieved. Namely, compositions containing a basic drug having an unpleasant taste and polyvinyl pyrrolidone and/or copolyvidone; and a method for relieving an unpleasant taste of a drug by adding polyvinyl pyrrolidone and/or copolyvidone. Compositions comprising (1) a basic drug, (2) polyvinyl pyrrolidone and/or copolyvidone and (3) propylene glycol and/or D-sorbitol; compositions comprising (1) a basic drug, (2) polyvinyl pyrrolidone and/or copolyvidone and (4) an antioxidant; and compositions comprising (1) a basic drug, (2) polyvinyl pyrrolidone and/or copolyvidone and (5) a coloring matter or a perfume having sulfate or sulfite.

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Description

Field of the Invention

[0001] The present invention relates to a composition or a method for reducing an unpleasant taste of a basic medicament having the unpleasant taste. In addition, the present invention relates to a composition alleviated in the defect of a composition containing a basic medicament, or a method for alleviating the defect.

Prior Art

[0002] Since oral administration of a medicament having an unpleasant taste such as bitter taste or numbness puts a burden on a patient and lowers compliance, various devices have been made to improve the taste of the medicament. When the medicament is solid such as tablets or granules, a bitter taste or the like can be masked in a relatively easy manner, for example, by coating or incorporation of the medicament in the matrix. For liquids, it is the common practice to conceal a taste of the medicament under a sweet taste substance such as sucrose, which is however, only a camouflage. A technique for essentially masking a bitter taste or the like is hardly known. Polyvinylpyrrolidone is known as a binder used for the preparation of tablets or the like. In JP-A 3-287535 and JP-A 4-18015, it is disclosed that a clear and stable aqueous solution is available by the addition of polyvinylpyrrolidone to a medicament sparingly soluble in water.

[0003] An object of the present invention is to alleviate an unpleasant taste of an oral medicament and moreover, to suppress the formation of a precipitate or decomposition product.

Disclosure of the Invention

[0004] The present invention is directed to a composition comprising a basic medicament having an unpleasant taste and polyvinylpyrrolidone and/or copolyvidone. In addition, it is also directed to a method for alleviating an unpleasant taste of a basic medicament having the unpleasant taste by adding polyvinylpyrrolidone and/or copolyvidone thereto.

[0005] In a further aspect of the present invention, there is also provided a composition comprising (1) a basic medicament, (2) polyvinylpyrrolidone and/or copolyvidone, and (3) propylene glycol and/or D-sorbitol.

[0006] In a still further aspect of the present invention, there is also provided a composition comprising (1) a basic medicament, (2) polyvinylpyrrolidone and/or copolyvidone, and (4) an antioxidant.

[0007] In a still further aspect of the present invention, there is also provided a composition comprising (1) a basic medicament, (2) polyvinylpyrrolidone and/or copolyvidone, and (5) a colorant or flavor containing a sulfuric acid or sulfurous acid group.

[0008] The present invention makes it possible to reduce an unpleasant taste of a basic medicament having the unpleasant taste and this is the first object of the present invention.

[0009] Addition of polyvinylpyrrolidone and/or copolyvidone increases analogues to the basic medicament with the passage of time. The second object of the present invention is to suppress this increase of analogues.

[0010] Addition of a colorant or flavor having a sulfuric acid or sulfurous acid group happens to form an insoluble precipitate of the basic medicament. To suppress the formation of this precipitate is also an object of the present invention.

[0011] The basic medicament having an unpleasant taste in the present invention means a medicament in which a proton exists as a positive charge under acidic conditions and which has an unpleasant taste. Examples include ticlopidine hydrochloride, azelastine hydrochloride, etilefrine hydrochloride, diltiazem hydrochloride, propranolol hydrochloride, indeloxazine hydrochloride, aminoguanidine hydrochloride and donepazil hydrochloride. Among these, effects are particularly remarkable when donepezil hydrochloride is used. Donepezil hydrochloride is chemically named (1-benzyl-4-(5,6-dimethoxyindanon-2-yl)methylpiperidine hydrochloride, and it is a remedy for Alzheimer's disease of a slight to a medium degree. The aqueous solution thereof has a sharp bitterness and numbness.

[0012] In the present invention, polyvinylpyrrolidone and/or the like reduces an unpleasant taste. Described specifically, a basic medicament having an unpleasant taste, which the medicament has been positively charged by a proton bound thereto in a solution, is trapped by two pyrrolidone groups, whereby contact of the basic medicament with a taste bud is sterically hindered.

[0013] In the present invention, polyvinylpyrrolidone is a linear polymer of 1-vinyl-2-pyrrolidone and that having an average molecular weight ranging from several thousand to several million can be used, with that having an average molecular weight of about 10000 to 2000000 is preferable.

[0014] In the Japanese Pharmacopoeia, polyvinylpyrrolidones having an average molecular weight of 25000, 40000 and 1200000 are described as polyvinylpyrrolidon K25, polyvinylpyrrolidone K30 and polyvinylpyrrolidone K90, respectively. They are easily available as Kollidon, the trade name. In the codices of Japan, USA and England, it is offi-

cially described as povidone, while in the codex of Europe, it is officially described as polyvidone. Both are embraced in the present invention.

[0015] In the present invention, copolyvidone is a (6:4) copolymer of a chain-structured vinyl pyrrolidone and vinyl acetate and for example, it is officially described in the codex of Europe as copolyvidone. In the present invention, polyvinylpyrrolidone and copolyvidone may be used either singly or in combination.

[0016] In the present invention, a ratio of a basic medicament having an unpleasant taste to polyvinylpyrrolidone and/or copolyvidone differs depending on the molecular weight or the like and cannot be determined in the wholesale manner. Polyvinylpyrrolidone having an average molecular weight of 40000 is usually added in an amount of 5 to 200 parts by weight, preferably 20 to 200 parts by weight or 100 to 200 parts by weight, more preferably 140 to 200 parts by weight, each based on 1 part by weight of the basic medicament such as donepezil hydrochloride. It is added in an amount of 5 to 100 parts by weight for the solubilization of an insoluble substance, and 50 to 200 parts by weight for masking of a bitter taste. The larger the molecular weight of polyvinylpyrrolidone, the less the amount of it to be added, while the smaller, the more the amount to be added.

[0017] Specific examples of the formulated preparation usable in the present invention include water-soluble liquids, syrups, elixirs, jellies, dry syrups, effervescent preparations, lemonades, aerosols, ophthalmic solutions, nasal drops, suppositories, cataplasmas, liniments, lotions and fine granules. Among these, syrups and jellies are particularly preferable. Syrups are each available by adding a sweetener such as sucrose, glucose, mannitol, xylitol, aspartame, saccharin or sorbitol and optionally a taste and smell corrigent. Jellies are usually available by adding, to the composition of the present invention, a gum and then a sweetener such as sucrose, glucose, mannitol, xylitol, aspartame, saccharin or sorbitol and optionally a taste and smell corrigent. The pH of the preparation is usually in the range of from 3 to 7.

[0018] The composition of the present invention in the form of an aqueous solution can be produced by weighing necessary amounts of a medicament and polyvinylpyrrolidone and/or copolyvidone, adding a sweetener, flavor or the like as needed and then dissolving the resulting mixture in water. When the medicament is donepezil hydrochloride, the dose is usually 1 to 20 mg/once.

[0019] The present invention provides a composition containing a basic medicament. The basic medicament includes the above-mentioned basic medicament having an unpleasant taste and the other basic medicaments. Examples thereof include acebutolol hydrochloride, aprindine hydrochloride, alprenolol hydrochloride, ambroxol hydrochloride, isoprenaline hydrochloride, imipramine hydrochloride, diphenidol hydrochloride, diltiazem hydrochloride, thiamine hydrochloride, trazodone hydrochloride, bunazosin hydrochloride, bunitrolol hydrochloride, ranitidine hydrochloride and midodrine hydrochloride.

[0020] In addition, the present invention provides a composition comprising (1) a basic medicament, (2) polyvinylpyrrolidone and/or copolyvidone, and (3) propylene glycol and/or D-sorbitol, or a composition comprising (1) a basic medicament, (2) polyvinylpyrrolidone and/or copolyvidone, and (4) an antioxidant. When the basic medicament and polyvinylpyrrolidone and/or copolyvidone are mixed, an amount of analogues of the basic medicament happens to increase upon storage. Addition of propylene glycol and/or D-sorbitol, or an antioxidant, however, can markedly suppress the increase of the analogues. Accordingly, the present invention also provides a method for suppressing the formation of analogues by the addition of such substances. Examples of the antioxidant usable in the present invention include sodium bisulfite, sodium sulfite, sodium pyrosulfite, cysteine, citric acid, sodium edetate, ascorbic acid and erythorbic acid. They may be used either singly or in combination.

[0021] The present invention further provides a composition comprising (1) a basic medicament, (2) polyvinylpyrrolidone and/or copolyvidone, and (5) a colorant or flavor containing a sulfuric acid or sulfurous acid group. Although the addition, to a basic medicament, of a colorant or flavor containing a sulfuric acid or sulfurous acid group happens to form an insoluble precipitate, the addition of polyvinylpyrrolidone and/or copolyvidone can remarkably suppress the formation of the insoluble precipitate. Accordingly, the present invention also provides a method for suppressing the formation of an insoluble precipitate of the basic medicament caused by the addition of a colorant or flavor containing a sulfuric acid or sulfurous acid group, by the addition of polyvinylpyrrolidone and/or copolyvidone. Examples of the colorant or flavor containing a sulfuric acid or sulfurous acid group include Food Red No. 102 (trisodium 2-hydroxyazonaphthalene-4',6,8-trisulfonate), Food Red No. 40, Food Red No. 3 (2',4',5',7'-tetraiodofluorescein disodium salt), Food Red No. 2 (trisodium 2-hydroxyazonaphthalene-3,4',6-trisulfonate), Food Blue No. 1 (disodium 3-[N-ethyl-N-[4-[[N-ethyl-N-(3-sulfonatobenzyl)amino]phenyl](2-sulfonatophenyl)methylene]-2,5-cyclohexadienyliden]ammoniomethyl]benzenesulfonate), Food Blue No. 2 (Acid Blue 74, disodium 2-(1,3-dihydro-3-oxo-5-sulfo-2H-indol-2-ylidene)-2,3-dihydro-3-oxo-1H-indole-5-sulfonate), Food Green No. 3 (disodium N-ethyl-N-[4-[[ethyl[(3-sulfophenyl)methyl]amino]phenyl](4-hydroxy-2-sulfophenyl)methylene]-2,5-cyclohexadien-1-ylidene]-3-sulfobenzenemethanaminiumhydroxide), Food Yellow No. 4 (trisodium 3-carbonato-5-hydroxy-1-(4-sulfonatophenyl)-1H-pyrazol-4-azo-4'-(benzenesulfonate)) and Food Yellow No. 5 (disodium 2-hydroxy-6-sulfonatonaphthalen-1-azo-(4'-benzenesulfonate)). They may be used either singly or in combination.

[0022] The composition according to the present inventi n has remarkable effects for alleviating an unpleasant

taste of a medicament and it is particularly useful when formulated into an orally administered liquid or jelly. It can remarkably suppress an increase, during storage, in the amount of the analogues of the basic medicament caused by the addition of polyvinylpyrrolidone and/or copolyvidone Moreover, it can prevent the formation of an insoluble precipitate of the basic medicament caused by the sulfuric acid or sulfurous acid group existing in the colorant or flavor.

[0023] Th above-described effects will be described more specifically by Tests given below.

Test 1

[0024] Examinees A and B held in their mouths Test solution 1 having, dissolved therein, 5 mg of donepezil hydrochloride and 700 mg of polyvinylpyrrolidone (average molecular weight: about 40000) per 5 g of the solution and Control solution 1 having, dissolved therein, 5 mg of donepezil hydrochloride per 5 g of the solution, and then evaluated the degree of a bitter taste and numbness. The results are shown in Table 1. It is apparent from Table 1 that the composition according to the present invention remarkably alleviates an unpleasant taste of the medicament.

Table 1

Examinee		A		B	
		Bitterness	Numbness	Bitterness	Numbness
Control solution 1		+++	+++	+++	+++
Test solution 1	just after the administration	±	±	±	±
	30 min after the administration	±	+	±	+

Test 2

[0025] Seven healthy examinees held in their mouths test solutions (Test solution 2, 3 and 4) having, dissolved therein, 5 mg of donepezil hydrochloride and each of 700 mg, 500 mg and 100 mg of polyvinylpyrrolidone (average molecular weight: 40000) per 5 g of the solution and Control solution 2 having, dissolved therein, 5 mg of donepezil hydrochloride and 3 g of sorbitol per 5 g of the solution. Five seconds later, they disgorged each of the solutions, rinsed their mouths with tap water and evaluated the degree of a bitter taste and numbness. Evaluation was conducted when they took the solution (when the test solution or control solution was held in the mouth), just after disgorging (before rinsing with water) and 5 minutes after disgorging (after rinsing with water). The evaluation standards and results are shown in Table 2. From Table 2, it is evident that the more the amount of polyvinylpyrrolidone added, the scores relating to the bitter taste and numbness increased, that is, the effects for masking an unpleasant taste heightened. The effects for alleviating the numbness are particularly remarkable compared with the control solution having sorbitol incorporated therein, suggesting that the effects of the present invention are not brought by false impression due to a sweet taste.

Table 2

Evaluati n standards :

Evaluation scores	Bitterness	Numbness
5	No feeling	No feeling
4	Dim feeling	Dim feeling
3	Slightly bitter	Slightly numb
2	Bitter	Numb
1	Very bitter	Very numb

Bitterness

Examinee	Test solution 2	Test solution 3	Test solution 4	Control solution 2
K.U.	5	4	2	4
H.A.	1	2	1	5
T.H.	3	2	2	5
M.K.	3	2	2	4
S.I.	3	2	2	3
K.K.	4	4	5	5
Y.I.	4	4	2	4
Avg	3.3	2.9	2.3	4.3

Numbness (wh n took the solution)

Examinee	Test solution 2	Test solution 3	Test solution 4	Control solution 2
K.U.	5	4	3	3
H.A.	5	5	4	5
T.H.	3	2	1	4
M.K.	5	3	3	3
S.I.	5	5	5	3
K.K.	5	5	5	5
Y.I.	5	4	3	4
Avg	4.7	4.0	3.4	3.9

Numbness (just after disgorging)

Examinee	Test solution 2	Test solution 3	Test solution 4	Control solution 2
K.U.	5	4	3	2
H.A.	5	5	3	5
T.H.	3	2	1	3
M.K.	5	5	4	2
S.I.	4	5	5	3
K.K.	5	5	5	5
Y.I.	4	3	3	4
Avg	4.4	4.1	3.4	3.4

Numbness (5 min after disgorging)

Examinee	Test solution 2	Test solution 3	Test solution 4	Control solution 2
K.U.	4	3	2	2
H.A.	5	4	2	5
T.H.	4	2	1	2
M.K.	5	5	4	3
S.I.	3	4	4	3
K.K.	5	5	4	5
Y.I.	4	3	3	4
Avg	4.3	3.7	2.9	3.4

Test 3

[0026] Samples obtained by incorporating 20% by weight of D-sorbitol into an aqueous solution containing 0.1% by weight of donepezil hydrochloride, obtained by incorporating 6% by weight of propylene glycol in the same aqueous solution and obtained by incorporating 5% by weight of polyvinylpyrrolidone to each of the above samples were stored at 60°C for 2 weeks or 1 month and the amount of analogues to donepezil hydrochloride was measured. The results are shown in Table 3.

[0027] It is apparent from Tabl 3 that the formation of the analogues is remarkably suppressed by incorporating D-sorbitol r propylene glycol.

Tabl 3

Relationship between the amount of analogue and stabilizer				
	term of storage 60°C	not incorporated (%)	D-sorbitol 20% incorporated (%)	propylene glycol 6% incorporated (%)
E2020 0.1%	2W	0.00	0.00	0.00
	1M	0.03	0.00	0.00
E2020 0.1% + PVP 5%	2W	0.36	0.10	0.00
	1M	0.61	0.27	0.19

Test 4

[0028] Storage test was conducted by storing a preparation, which had been formulated as shown in Table 4, at 60°C for 2 weeks or at 45°C for 1 month. As a result, no analogues to donepezil hydrochloride was detected from the sample added with sodium bisulfite.

Table 4

Fillers	Control mg/5ml	Test sample mg/5ml
Donepezil hydrochloride	5	5
Sodium bisulfite		1
70% D-sorbitol	1785	1785
Povidone K30	250	250
Citric acid	10	10
Sodium citrate	proper amount	proper amount
Sodium benzoate	5	5
Food Red No.40	0.05	0.05
Strawberry flavor	15	15
Purified water	proper amount	proper amount
Total	5 ml	5 ml
Total amount of analoges (60°C/2W)	0.60%	0%
Total amount of analoges (45°C/1M)	0.46%	0%

Test 5

[0029] From the formulation similar to that shown in Table 5 except that povidone is not added, a precipitate appeared under the storage conditions at a room temperature or in a cool place (4°C).

Table 5

Fillers	Prescription 1 mg/5ml	Prescription 2 mg/5ml
Donepezil hydrochloride	5	5
70% D-sorbitol	1785	1785
Povidone K30	250	250

Table 5 (continued)

Fill rs	Prescription 1 mg/5ml	Prescription 2 mg/5ml
Citric acid	10	10
Sodium citrate	proper amount	proper amount
Sodium benzoate	5	5
Food Red No.40	0.05	0
Sunset Yellow	0	0.02
Strawberry flavor	15	0
Orange flavor	0	15
Purified water	proper amount	proper amount
Total	5 ml	5 ml

Examples

[0030] The present invention will hereinafter be described more in detail in accordance with Examples, but the present invention should not be limited by them.

Example 1

[0031] A composition of the present invention was obtained by dissolving 50 mg of donepezil hydrochloride and 7.00 g of polyvinylpyrrolidone in 42.95 g of water.

Example 2

[0032] In 400 g of purified water were dissolved 500 mg of donepezil hydrochloride, 70 g of polyvinylpyrrolidone (average molecular weight: about 40000), 100 g of sorbitol, 1 g of saccharin sodium, 1 g of sodium citrate and 1.5 g of sodium beuzoate, followed by the addition of citric acid to adjust the pH of the resulting solution to 5.0. The total volume of the solution was adjusted to 500ml, and 5 g portions of the solution were put into vials.

Example 3

[0033] Povidone (2.5 g, trade name: Kollidon 30) was added to purified water in portions to dissolve. A 70% D-sorbitol solution (17.9 g), 100 mg of citric acid (100 mg) and benzoic acid (50 mg) were added to the resulting solution to dissolve. Donepezil hydrochloride (50 mg) was then added to the resulting solution to dissolve, followed by the addition of sodium citrate to adjust the pH of the resulting solution to 3.9. To the resulting solution were further added 0.5 mg of Food Red No. 40 and 150 mg of strawberry flavor. Purified water was added to give a total volume of 50 ml. Into vials were pipetted 5 ml portions of the resulting solution.

Example 4

[0034] Povidone (2.5 g, trade name: Kollidon 30) was added to purified water in portions to dissolve. A 70% D-sorbitol solution (17.9 g), 100 mg of citric acid (100 mg) and benzoic acid (50 mg) were added to the resulting solution to dissolve. Donepezil hydrochloride (50 mg) was then added to the resulting solution to dissolve, followed by the addition of sodium citrate to adjust the pH of the resulting solution to 3.9. To the resulting solution were further added 0.2 mg of Sunset Yellow and 150 mg of orange flavor, followed by the addition of purified water to give a total amount of 50 ml. Into vials were pipetted 5 ml portions of the resulting solution.

Example 5

[0035] Purified water was added to 50 mg of donepezil hydrochloride, 2.5 g of polyvinylpyrrolidone and 10 g of D-sorbitol to dissolve and the total volume was adjusted to 50 ml.

Example 6

[0036] Purified water was added to 50 mg of donepezil hydrochloride, 2.5 g of polyvinylpyrrolidone and 3 g of propylene glycol to dissolve and the total volume was adjusted to 50 ml.

Example 7

[0037] Povidone (2.5 g, trade name: Kollidon 30) was added to purified water in portions to dissolve. In the resulting solution, A 70% D-sorbitol solution (17.9 g), citric acid (100 mg), sodium benzoate (50 mg) and sodium bisulfite (10 mg) were added to the resulting solution to dissolve. Donepezil hydrochloride (5 mg) was added to the resulting solution to dissolve, followed by the addition of sodium citrate to adjust its pH to 3.9. To the resulting solution were further added Food Red No. 40 (0.5 mg) and 150 mg of strawberry flavor, followed by the addition of purified water to give a total amount of 50 ml. Into vials were pipetted 5 ml portions of the resulting solution.

Example 8

[0038] Povidone (2000 g, trade name: Kollidon 30) was added in portions to 15L of purified water to dissolve. To the resulting solution was added 13280 g of a 70% D-sorbitol solution, followed by stirring for 30 minutes. After the complete dissolution of copolydone was confirmed, 400 g of a 20% citric acid solution and 400 g of a 10% sodium benzoate solution were added to the reaction mixture to dissolve. A solution of donepezil hydrochloride (40 g) dissolved in 1000 g of a 70% D-sorbitol solution was added thereto, followed by stirring. A solution of methylparaben (40 g) dissolved in 2400 g of propylene glycol was further added thereto, followed by stirring. A 10% sodium citrate solution was added to the resulting mixture to adjust the pH thereof to 3.9. To the resulting solution were further added a 0.2% solution (200 g) of Food Red No. 40 and 120 g of strawberry flavor, followed by the addition of purified water to give a total amount of 40 L. The resulting mixture was stirred. The resulting solution was filtered through a 0.22 μm filter and 5 ml portions were pipetted into aluminum stick packages.

Claims

1. A pharmaceutical composition comprising (1) a basic medicament having an unpleasant taste and (2) at least one selected from polyvinylpyrrolidone and copolyvidone.

2. The composition as claimed in Claim 1, which comprises (1) 1 part by weight of the basic medicament having an unpleasant taste and (2) 5 to 200 parts by weight of polyvinylpyrrolidone and/or copolyvidone.

3. A method for alleviating an unpleasant taste of a basic medicament having the unpleasant taste by adding thereto at least one selected from polyvinylpyrrolidone and copolyvidone.

4. The composition as claimed in Claim 1 or 2, which is in the form of syrups, jellies, dry syrups, liquids, effervescent preparations, lemonades, elixirs, liniments or fine granules.

5. A composition comprising (1) a basic medicament, (2) at least one selected from polyvinylpyrrolidone and copolyvidone, and (3) at least one selected from propylene glycol and D-sorbitol.

6. A method for suppressing the formation of analogues to (1) a basic medicament caused by the addition of (2) polyvinylpyrrolidone or copolyvidone, by adding at least one selected from (3) propylene glycol and D-sorbitol.

7. A composition comprising (1) a basic medicament, (2) at least one selected from polyvinylpyrrolidone and copolyvidone, and (4) an antioxidant.

8. The composition as claimed in Claim 7, wherein the antioxidant (4) is selected from the group consisting of sodium bisulfite, sodium sulfite, sodium pyrosulfite, cysteine, citric acid, sodium edetate, ascorbic acid and erythorbic acid.

9. A method for suppressing the formation of analogues to (1) a basic medicament caused by the addition of (2) polyvinylpyrrolidone or copolyvidone by adding (4) an antioxidant.

10. A composition comprising (1) a basic medicament, (2) at least on selected from polyvinylpyrrolidone and copolyvid ne, and (5) a col rant r flavor containing a sulfuric acid or sulfurous acid group.

11. The composition as claimed in Claim 10, wherein the colorant or flavor (5) containing a sulfuric acid or sulfurous acid group is selected from the group consisting of Food Red No. 102, Food Red No. 40, Food Red No. 3, Food Red N . 2, Food Blue No. 1, Food Blu No. 2, Food Green No. 3, Food Yellow No. 4 and Food Yellow No. 5.

12. A method for suppressing the formation of an insoluble precipitate of (1) a basic medicament caused by the addition of (5) a colorant or flavor containing a sulfuric acid or sulfurous acid group, by adding (2) at least one selected from polyvinylpyrrolidone and copolyvidone.

13. The composition as claimed in Claim 1, wherein the medicament is donepezil hydrochloride.

INTERNATI NAL SEARCH REPORT

International application No.
PCT/JP99/04616

A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl[6] A61K47/32

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int. Cl[6] A61K47/32

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	JP, 10-36292, A (Taisho Pharmaceutical Co., Ltd.), 10 February, 1998 (10.02.98) (Family: none)	1-9
X	JP, 60-204712, A (SSP CO., LTD.), 16 October, 1985 (16.10.85) (Family: none)	1-6
X	JP, 3-5418, A (KOWA COMPANY, LTD), 11 January, 1991 (11.01.91) (Family: none)	1-4
X	JP, 9-143100, A (SUMITOMO PHARMACEUTICALS COMPANY LIMITED), 03 June, 1997 (03.06.97) (Family: none)	1-4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
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Date of the actual completion of the international search	Date of mailing of the international search report
15 November, 1999 (15.11.99)	24 November, 1999 (24.11.99)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)